In Utero Dioxin Exposure and Thyroid Hormone Levels in the Seveso Second Generation

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Introduction
In animal studies, prenatal and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters thyroid homeostasis and thyroid hormone concentrations.[1-3] Limited epidemiologic evidence suggests in utero exposure to TCDD is associated with altered thyroid function in neonates and children. Studies in the Netherlands found higher thyroid stimulating hormone (TSH) in infants ≤3 months in relation to elevated breast milk TEQ.[4,5] While these results suggest a hypothyroid effect of dioxins, positive associations noted between the TEQ in breast milk, PCDD/Fs in the placenta, and total thyroxine (TT4) suggest that dioxins may alter the negative feedback system that maintains thyroid hormone homeostasis [5,6]. Two small studies (n=33-37) of children ~2 years old found no significant association between breast milk TEQ and TT4, total triiodothyronine (TT3), or TSH [7,8], while a larger study reported elevated TT3 at age 2 (n=136) and 5 years (n=149) among girls, but not boys, with higher placental TEQ (>15 pg/g lipids).[9]

The Seveso Women’s Health Study (SWHS) of women exposed to a single high dose of TCDD during or before their child-bearing years is unique.[10] Initial, individual-level TCDD exposure measures are available for this first-generation cohort.[11,12] Nearly 40 years after the explosion, data collection to follow up the second generation of the SWHS cohort is complete. We aim to examine the relationship of in utero TCDD exposure with thyroid function among all SWHS children. Here, we report preliminary results to date for adult children 18 years and older.

Materials and methods
We included 429 children who were 18+ years with complete follow-up data, including a fasting blood draw. Serum levels of TT4, free thyroxine (FT4), free triiodothyronine (FT3), and TSH were measured using immunoassays (Roche Diagnostics, Mannheim Germany). We defined in utero TCDD exposure in two ways: 1) initial TCDD concentration measured in maternal serum collected soon after the explosion, and 2) TCDD estimated at pregnancy. TCDD levels were log-transformed and included as a continuous variable. TSH was log-transformed to approximate a normal distribution; FT3, FT4 and TT4 were normally distributed and expressed on the arithmetic scale. We used linear regression to examine the relation of serum TCDD with thyroid hormones. For all outcomes, we considered effect modification by sex.

Results and discussion
The 429 children (223 female, 206 male) were an average of 28.6 (±6.0) years of age at follow-up. In utero TCDD exposure based on initial maternal serum TCDD level is high (median=53.47 ppt), with a wide range (3-5,710). A 10-fold increase in initial maternal TCDD concentration was negatively associated with FT3 (adj-β=-0.06, 95% CI -0.13, 0.01), but not FT4 (adj-β=-0.19, 95% CI -0.50, 0.12), TT4 (adj-β=-0.18, 95% CI -0.52, 0.17) or TSH (adj-
\[ \beta = 7.0\%, \text{95\% CI} -5.0, 20.4). \] Stratifying by child sex, initial maternal TCDD concentration was positively associated with TSH among daughters (adj-\[ \beta = 18.6\%, \text{95\% CI} -1.2, 42.4\]), but not sons (adj-\[ \beta = -4.6\%, \text{95\% CI} -17.7, 10.6\]) \(p\)-int=0.08).

Fully adjusted results for the complete Seveso second generation cohort, including the children who are less than 18 years, will be presented. In addition, we will present results using TCDD exposure extrapolated to the pregnancy.

These preliminary results suggest \textit{in utero} exposure to TCDD, a potent endocrine-disrupting compound, may alter thyroid function later in life. In this case we observe decreased FT3 levels and increased TSH levels in daughters exposed to TCDD.

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\textbf{References}
